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ORIGINAL RESEARCH

Trajectories of Efficacy and Cognitive Function During Electroconvulsive Therapy Course in Young Adults with Treatment-Resistant Depression

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Objective: Little is known about the effectiveness and cognitive side-effects of electroconvulsive therapy (ECT) in young adults with treatment-resistant depression (TRD). The primary aim of this prospective longitudinal observational trial was to examine the clinical features and cognitive outcomes of young adults with TRD undergoing ECT.

Methods: Changes in depressive symptoms and objective and subjective cognitive function were assessed using repeated evaluation at baseline, after each ECT session, and at one-month follow-up using the Montgomery-Äsberg Depression Rating Scale (MADRS) and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Forward Digital Span Test (FDST), and part of the Columbia Subjective Side Effects Schedule.

Results: Of 41 inpatients, 35 (85.4%) and 12 (29.3%) met the criteria for response and remission after ECT, respectively. The greatest clinical improvements occurred during the first 3–4 ECT sessions. While 34 patients reported subjective cognitive impairment increased with ECT, immediate and delayed memory (RBANS) significantly increased after ECT, consistent with FDST results. Objective cognition significantly improved during follow-up, but subjective cognition remained impaired.

Conclusion: ECT is effective in young adults with TRD. Although subjective cognitive impairment increased during treatment, objective cognitive impairments were not observed.

Keywords: electroconvulsive therapy, young adults, cognitive function, treatment-resistant depression

Introduction

Depressive disorder is common, debilitating, and significantly impacts the quality of life of affected individuals.[1,2] There have been many studies on depression in children, adolescents and the elderly[3–8] but relatively few in young adults,[9–11] despite them having different social and neurobiological profiles.[12,13] Almost 40% of patients experience their first episode of depression before 20 years of age.[2] Their clinical course tends to fluctuate, with multiple recurrences in the context of life transitions.[12]

Depressive disorder that does not respond satisfactorily to treatment is referred to as treatment-resistant depression (TRD).[14] Although TRD episodes are most commonly associated with major depressive disorder, they are also seen in the depressed phase of bipolar disorder;[15] indeed, responses are not sustained in over 30% of individuals receiving treatment for unipolar depression (UPD) or bipolar depression (BPD).[16–18] TRD is therefore a significant public health problem characterized by extensive disability, increased suicide attempts, and higher medical costs.[16,19]

Electroconvulsive therapy (ECT) has been used in clinical practice for over 80 years and is widely considered the most reliable therapy for TRD.[20–22] ECT is associated with a reduced risk of suicide in the year after discharge.[23] While there is strong evidence supporting the efficacy of ECT in middle-aged and older adults,[24,25] little is known about its

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efficacy and cognitive side-effects in younger adults (aged 18–30) with TRD. Previous studies have suggested that ECT in young adults improves clinical outcomes during the acute treatment phase.[26,27] Since TRD and non-TRD may differ clinically and biologically,[28,29] it still needs to be clarified whether young adult with TRD adequately respond to ECT, and the side-effects and prognosis require characterization.

This study therefore had the primary objective of establishing the clinical effectiveness, speed of response, and cognitive outcomes of ECT in young adult patients with TRD. The exploratory objective was to investigate differences in ECT responses in young adults with UPD and BPD. To better answer the primary objective, we used repeated evaluation after each ECT to detail the changes in depressive symptoms and cognitive function during the entire ECT process.

Materials and Methods

This longitudinal observational trial was conducted at Renmin Hospital of Wuhan University (Mental Health Center of Hubei Province, Wuhan, Hubei, China) in accordance with the Declaration of Helsinki (revised edition, 2013).[30] The Human Ethics Committee of Renmin Hospital of Wuhan University approved the study protocol. Patients or their legal guardians provided informed consent and could withdraw from the trial at any time for any reason. This report follows the STROBE statement.[31]

Trial Design

We recruited 41 patients to Cohort 1, the "main" cohort. Routine symptom and detailed cognitive function examinations were performed at baseline, after the entire ECT course, and one month later. To map the detailed trajectory of symptoms and subjective memory impairment (SMI) during ECT treatment, depressive symptom and SMI evaluations were performed after each ECT session.

Cohort 2 was used to detect changes in objective memory function with ECT and represented a 23-patient subset of Cohort 1. The forward digital span test (FDST),[32] a simple and widely used tool of verbal short-term and working memory, was assessed after each ECT session. Considering potential practice effects, we recruited 15 healthy controls (HCs) matched for age, sex, and years of education, who received twelve FDSTs at the same test frequency (three times per week) as a longitudinal benchmark. Figure 1 shows the trial flow chart and study design.

Participants and Inclusion and Exclusion Criteria

Sixty-two inpatients were recruited from March 1st, 2021 to January 31st, 2022. The inclusion criteria were (1) participants aged between 18 and 30 years; (2) ability to provide informed consent; (3) meeting ICD-10[33] criteria for the diagnosis of major depression or bipolar disorder current episode depressive, with or without psychotic features (F31.3, F31.4, F31.5, F32, F33) using the Mini International Neuropsychiatric Interview (MINI);[34] (4) meeting the definition of TRD: patients with UPD required a minimum of two prior treatment failures and confirmation of prior adequate dose and duration,[15] while patients with BPD required no response to treatment after 12 weeks of treatment or a well-documented failure to respond to at least two trials of antidepressants or an antidepressant and a mood stabilizer;[35] and (5) scored ≥20 on the Montgomery-Äsberg Depression Rating Scale (MADRS).[36] We excluded patients if they: (1) failed to respond to earlier ECT; (2) had received ECT over the previous three months; (3) patients with manic episodes and mixed characteristics of BPD or scored ≥6 on the Young Manic Rating Scale (YMRS);[37] (4) had a lifetime diagnosis of unstable, serious comorbidities or a history of epilepsy; (5) were pregnant or women without adequate contraception; and (6) were in other clinical studies or were unsuitable for participation as assessed by the investigators.

Age-, sex-, and education-matched HCs were recruited through advertisements. They were required to be in good physical health with no personal or first-degree family history of a psychiatric disorder, significant medical illness, psychotropic medication use, or use of other medications that could interfere with neuropsychological function.

ECT Procedures

All participants received a standard pre-ECT clinical assessment including a full physical examination, laboratory analyses, electrocardiogram, electroencephalogram (EEG), and monitoring for any risks or contraindications to anesthesia and/or ECT. All individuals included in the trial did not have any clinically significant abnormalities on this assessment. Patients received bitemporal electrode placement ECT which was performed three times per week using a Thymatron IV device (Somatics,

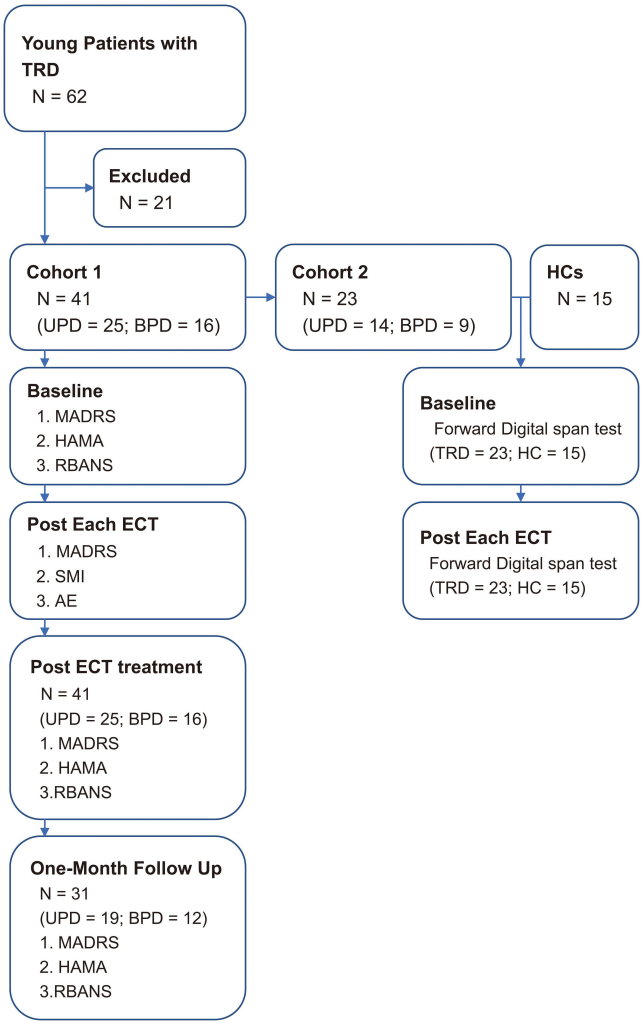

Figure 1 Study flow chart.
Abbreviations: TRD, treatment-resistant depression; UPD, unipolar depression; BPD, bipolar depression; HC, healthy control; ECT, electroconvulsive therapy; MADRS, Montgomery-Äsberg Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

LLC). Seizure threshold was determined at the first ECT session starting at a dose level of 50mC (or 10% of machine energy) and titrated upwards till a seizure of at least 15s was induced. Subsequent ECT treatments were administered at 1.5 times seizure threshold (or one level higher).[38] General anesthesia was induced with propofol (about 2 mg/kg) and myorelaxation with succinylcholine (about 1 mg/kg) and atropine (0.5 mg) before each session. Doses of propofol and succinylcholine were adjusted as needed in subsequent sessions. Orientation recovery tests after each ECT session were used to measure recovery. The decision to discontinue ECT was made by the patient's psychiatrist after considering 1) reduced potential benefit of ECT; 2) side effects; 3) completed 12 ECT sessions; 4) patient preference; and 5) other medical considerations.

Pharmacotherapy

Individualized pharmacological regimens were determined by the patients' psychiatrists. Patients maintained their previously prescribed antidepressants and antipsychotics during the trial. Anticonvulsant drugs, mood stabilizers, and benzodiazepines were discontinued during the entire course of ECT. Single-dose short half-life benzodiazepines were used as necessary when patients became agitated or felt anxious. When patients suffered from insomnia, nonbenzodiazepines were temporarily prescribed.

Measurement Tools and Visit Schedule

Efficacy Measures

The MADRS was used to evaluate depressive symptoms and was performed at baseline, after each ECT session, and at one-month follow-up. A response was defined as a decrease in total MADRS score >50% from baseline to the end of treatment, and remission was defined as a total MADRS score <10 at the end of the treatment.[39] The MADRS was also divided into four factors: 1) cognitive-pessimism; 2) affective; 3) cognitive-anxiety; and 4) vegetative.[40] The Hamilton Anxiety Rating Scale (HAMA)[41] was used to evaluate the anti-anxiety effect of ECT and was performed at baseline, after the course of ECT, and at one-month follow-up. The HAMA was also divided into somatic anxiety and psychic anxiety.

Safety Measures

Any adverse events (AEs)/serious AEs (SAEs) or patients who dropped out for any reason were recorded.

Cognitive Measures

In Cohort 1, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[42] was performed at baseline, after the course of ECT, and at one-month follow-up to assess objective cognitive function. SMI was assessed with the cognitive component of the Columbia Subjective Side Effects Schedule (CSSES)[43] after each ECT: "have you had memory problems since ECT?" This item was scored on a 4-point Likert-type scale where 0 = none, 1 = mild, 2 = moderate, and 3 = severe.

Objective memory function changes were assessed in Cohort 2. Given that most cognitive tests are complex and can take a long time to perform, tests should be simple and reliable to perform. Therefore, the FDST was chosen to evaluate memory function after each ECT session. Twelve FDSTs were performed on HCs at the same test frequency (three times per week) to provide a longitudinal benchmark.

All assessments in patients were administered 24 hours after every ECT session to avoid possible acute treatment effects.

Sample Size

The sample size was calculated using G*Power software (ver. 3.1.9.7).[44] We expected to detect a moderate effect size (Cohen's $f = 0.25$) of MADRS in seven visits (the mean number of ECT treatment is approximately six plus a baseline visit) with a power of 0.85, α of 0.05 (two-sided), and obtained a sample size of 42.

Statistical Methods

Missing Data

Longitudinal analyses did not require input of missing values, because the statistical methods (mixed model for repeated measures (MMRM) and cumulative link mixed model for repeated ordinal outcomes (CLMM)) could accommodate missing data.

Descriptive Analyses

For baseline comparisons, continuous demographic and clinical characteristics were compared using Welch's two-sample *t*-test, and categorical characteristics were analyzed using Fisher's exact test.

Efficacy Analyses

The primary outcome was the change in MADRS at post-treatment visit from baseline. Secondary outcomes were changes in the MADRS subscales, HAMA and its subscales. MMRM analyses were performed to estimate the dynamics of these continuous outcomes and compare the between-subgroup differences between the UPD and BPD subgroups. In general, the MMRM model included subgroup, visit (as a categorical variable), and the subgroup*visit interaction as fixed factors. Baseline values, fluoxetine, and chlorpromazine equivalent dose were included as covariates to control for potential bias from baseline status and the effect of pharmacotherapy. An unstructured covariance matrix will be used to model the within-subject correlation, and the Kenward-Roger approximation method was used to calculate the denominator degrees of freedom. Treatment effects were reported using MMRM least squares (LS) means and associated 95% confidence intervals (95% Cis). Pair-wise comparisons were adjusted using Tukey's method.

Cognitive Analyses

For RBANS and FDST, similar MMRM analyses were also performed. As SMI was an ordinal variable, CLMM was performed, subgroup, visit, and the subgroup*visit interaction as included as fixed factors, and odds ratios (Ors) and their 95% Cis were used to examine whether the change in SMI increased with ECT treatment. Age, charge, and pulse width[45,46] were included as covariates in both MMRM and CLMM to control for potential confounders.

Statistical Software

All statistical tests were carried out using R version 4.1.0 (R Project for Statistical Computing) within RStudio version 1.4.1106 (RStudio) for Windows. *LmerTest* package[47] was used for MMRM analyses, *ordinal* package[48] was used for CLMM, *effectsize* package[49] was used to calculate the effect sizes, and *ggplot2* package[50] was used for visualization.

Results

Participant Flow and Characteristics

Figure 1 shows the participant flow. For the main cohort, 62 patients were enrolled: 20 screen failures were excluded after entry, and 42 patients completed the visits after ECT treatment. Unfortunately, one patient withdrew informed consent after the trial completed; as a result, the final sample size for analysis was 41. Twenty-three patients also participated in Cohort 2. Descriptive data are presented in Table 1, and Table S1 presents the comparisons between the UPD and BPD subgroups.

Table 1 Descriptive Data of Included Subjects

Parameter	Cohort 1	Cohort 2		
	TRD	TRD	HC	p^a
Subject, *n*	41	23	15	
Sex, Female/Male	24/17	15/8	10/5	1.000
Age, years, *mean (s.d.)*	22.0 (3.9)	22.4 (3.2)	24.6 (4.0)	0.084
Education years, *mean (s.d.)*	14.0 (2.0)	15.0 (1.5)	15.0 (2.0)	0.943
Clinical characteristics				
UPD/BPD, *n*	25/16	14/9	NA	–
Age of onset, years, *mean (s.d.)*	16.1 (4.1)	15.8 (3.9)	NA	–
Total disease course, years, *mean (s.d.)*	6.0 (3.1)	6.6 (3.6)	NA	–
With psychotic features, yes/no	11/30	6/17	NA	–
MADRS, *mean (s.d.)*	37.2 (7.2)	39.1 (7.0)	NA	–
HAMA, *mean (s.d.)*	21.2 (8.3)	21.3 (9.1)	NA	–
ECT characteristics				
History of ECT, yes/no	5/36	3/20	NA	–
Seizure threshold, mC, *mean (s.d.)*	68.3 (31.5)	72.5 (38.9)	NA	–
ECT number, *mean (s.d.)*	6.6 (2.7)	6.4 (2.7)	NA	–
Total charge, mC, *mean (s.d.)*	580.0 (316.5)	601.8 (352.6)	NA	–
Medication, yes/no	41/0	23/0	NA	–
SSRIs, yes/no	24/17	17/6	NA	–
SNRIs, yes/no	12/19	1/22	NA	–
Other antidepressants, yes/no	10/31	5/18	NA	–
Moodstabilizer, yes/no	33/8	19/4	NA	–
Fluoxetine equivalent dose, *mean (s.d.)*	36.4 (20.1)	31.2 (18.1)	NA	–
Atypical antipsychotics, yes/no	35/6	20/3	NA	–
Chlorpromazine equivalent dose, *mean (s.d.)*	170.2 (155.0)	173.8 (186.1)	NA	–
Baseline Cognitive Functions				
RBANS total score, *mean (s.d.)*	452.0 (44.6)[b]			
Forward Digital Span Test, *mean (s.d.)*		8.3 (1.4)	8.8 (1.7)	0.320

Notes: [a]For categorical data, Fisher exact test was used, for numerical data, asymptotic two-Sample Welch's *t*-test was used. [b]Three UPDs did not complete the baseline RBANS tests.

Abbreviations: TRD, treatment-resistant depression; UPD, unipolar depression; BPD, bipolar depression; HC, health control; ECT, electroconvulsive therapy; s.d., standard deviation; MADRS, Montgomery-Asberg Depression Rating Scale; HAMA, Hamilton Anxiety Scale; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

Forty-one participants received a total of 272 ECTs, and 31 (75.6%) completed the one-month follow-up visit. Six patients ended ECT without a clinical response and less than 12 treatments due to fever, headache, and dissatisfaction with the efficacy. Ten patients dropped out at one-month follow-up. There were no significant differences in response/remission rates at the post-ECT visit between completers and dropout patients (see Table S2).

Efficacy Results

The LS mean change in total MADRS score from baseline to the end of treatment was −24.9 (95% CI = −27.9, −21.9), Cohen's f = 1.19 (90% CI = 1.02, 1.31). Thirty-five (85.4%) and 12 (29.3%) patients met the criteria for response and remission after ECT. In subgroup analyses, the difference in response rate and remission rate between patients with UPD (80.0% and 28.0%) and BPD (93.8% and 31.3%) were non-significant (Fisher's exact test, p = 0.376 and 1.000). Anxiety mirrored the depressive symptoms. In subgroup analyses, the antidepressant and anti-anxiety effects of CBT were similar. The reduction in total MADRS total score and its two subscales (cognitive pessimism and affective) and the HAMA subscale (somatic anxiety) were slightly but significantly larger in the UPD subgroup than the BPD subgroup at the follow-up visit (all adjusted P-values (Tukey's method) <0.05, see Table S3). However, BPD patients received significantly more ECT sessions than the UPD patients.

At one-month follow-up, 16/31 (51.6%) and 8/31 (25.8%) patients met the criteria for response and remission. In subgroup analyses, the differences in response rates and remission rates between patients with UPD (57.9% and 36.8%) and BPD (41.7% and 8.3%) were not significant (Fisher's exact test, p = 0.473 and 0.199). Details of the MADRS, HAMA, and their subscale estimates are presented in Table 2, Figure 2, and Figures S1 and S2.

As shown in Figure 3, Table S3, and Figure S3, the effect size of MADRS trajectories over the course of ECT was large. There were steep trajectories for MADRS and its four subscales after 3–4 ECTs, and the reduction from baseline was statistically significant after the first ECT. In subgroup analyses, the MADRS trajectories for both UPD and BPD patients were similar, except for the "vegetative" subscale, whose reduction in the UPD subgroup was significantly quicker than in the BPD group at visits 2–6 (adjusted p-values (Tukey's method) <0.05, see Table S3).

Table 2 Estimated Least Squares Mean Effect Size of MADRS and HAMA Based on MMRM

	TRD	Subgroup Analyses			
		UPD	BPD	Between-Group Difference	
Change from baseline	**mean [95% CI]**	**mean [95% CI]**	**mean [95% CI]**	**mean [95% CI]**	***p***
MADRS					
Total score					
Post ECT	−24.9 [−27.9, −21.9]***	−25.3 [−29.1, −21.4]***	−24.5 [−29.6, −19.4]***	0.8 [−6.1, 7.6]	0.823
Follow up	−15.5 [−18.9, −12.1]***	−19.6 [−24.0, −15.1]***	−11.4 [−17.1, −5.8]***	8.1 [0.6, 15.6]	0.034*
Cognitive Pessimism					
Post ECT	−12.3 [−13.9, −10.7]***	−12.7 [−14.8, −10.6]***	−11.9 [−14.6, −9.2]***	0.8 [−2.9, 4.5]	0.665
Follow up	−8.6 [−10.4, −6.8]***	−11.1 [−13.4, −8.7]***	−6.2 [−9.1, −3.2]***	4.9 [0.9, 8.9]	0.017*
Affective					
Post ECT	−6.7 [−7.8, −5.6]***	−6.5 [−7.9, −5.1]***	−7.0 [−8.8, −5.1]***	−0.5 [−2.9, 2.0]	0.697
Follow up	−4.4 [−5.6, −3.2]***	−5.8 [−7.4, −4.2]***	−3.0 [−5.0, −0.9]**	2.9 [0.2, 5.6]	0.037*
Cognitive Anxiety					
Post ECT	−4.1 [−4.8, −3.4]***	−4.0 [−4.9, −3.2]***	−4.2 [−5.4, −3.1]***	−0.2 [−1.7, 1.4]	0.813
Follow up	−1.9 [−2.7, −1.1]***	−2.1 [−3.2, −1.1]***	−1.6 [−2.9, −0.3]*	0.5 [−1.2, 2.3]	0.533
Vegetative					
Post ECT	−4.7 [−5.3, −4.1]***	−5.1 [−5.9, −4.4]***	−4.3 [−5.3, −3.3]***	0.8 [−0.5, 2.1]	0.231
Follow up	−2.6 [−3.3, −2.0]***	−3.2 [−4.1, −2.3]***	−2.0 [−3.1, −1.0]***	1.2 [−0.3, 2.6]	0.113

(*Continued*)

Table 2 (Continued).

	TRD	Subgroup Analyses			
		UPD	BPD	Between-Group Difference	
Change from baseline	**mean [95% CI]**	**mean [95% CI]**	**mean [95% CI]**	**mean [95% CI]**	***p***
HAMA					
Total score					
Post ECT	−12.2 [−14.6, −9.8]***	−12.6 [−15.7, −9.5]***	−11.8 [−16.0, −7.7]***	0.7 [−4.8, 6.2]	0.790
Follow up	−7.5 [−10.2, −4.8]***	−9.6 [−13.1, −6.0]***	−5.5 [−9.9, −1.0]*	4.1 [−1.9, 10.1]	0.178
Somatic Anxiety					
Post ECT	−7.3 [−8.7, −5.8]***	−7.7 [−9.5, −5.9]***	−6.8 [−9.2, −4.4]***	0.9 [−2.3, 4.1]	0.581
Follow up	−4.9 [−6.5, −3.2]***	−6.7 [−8.8, −4.6]***	−3.0 [−5.7, −0.4]*	3.7 [0.1, 7.2]	0.044*
Psychic Anxiety					
Post ECT	−4.9 [−6.1, −3.8]***	−4.9 [−6.4, −3.4]***	−5.0 [−7.0, −3.0]***	−0.1 [−2.7, 2.6]	0.968
Follow up	−2.7 [−4.0, −1.4]***	−3.0 [−4.7, −1.2]**	−2.4 [−4.5, −0.2]*	0.6 [−2.4, 3.5]	0.702

Notes: Degrees-of-freedom method: Kenward-Roger approach. P value adjustment: Tukey method, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
Abbreviations: MMRM, mixed model for repeated measures; TRD, treatment-resistant depression; UPD, unipolar depression; BPD, bipolar depression; CI, confidence interval; MADRS, Montgomery-Asberg Depression Rating Scale; HAMA, Hamilton Anxiety Scale.

Cognitive Results

As shown in Table 3 and Figure 4, at the post-ECT visit, there were no significant changes in total RBANS score nor the visuospatial/constructional, language, and attention subscales. There was a significant post-ECT increase in two RBANS subscales (immediate memory and delayed memory). At one-month follow-up, there was a significant increase in total RBANS score and the immediate memory, attention, and delayed memory subscales. Subgroup analysis suggested that the UPD subgroup contributed most to these changes, but the between-subgroup differences were not statistically significant after correction.

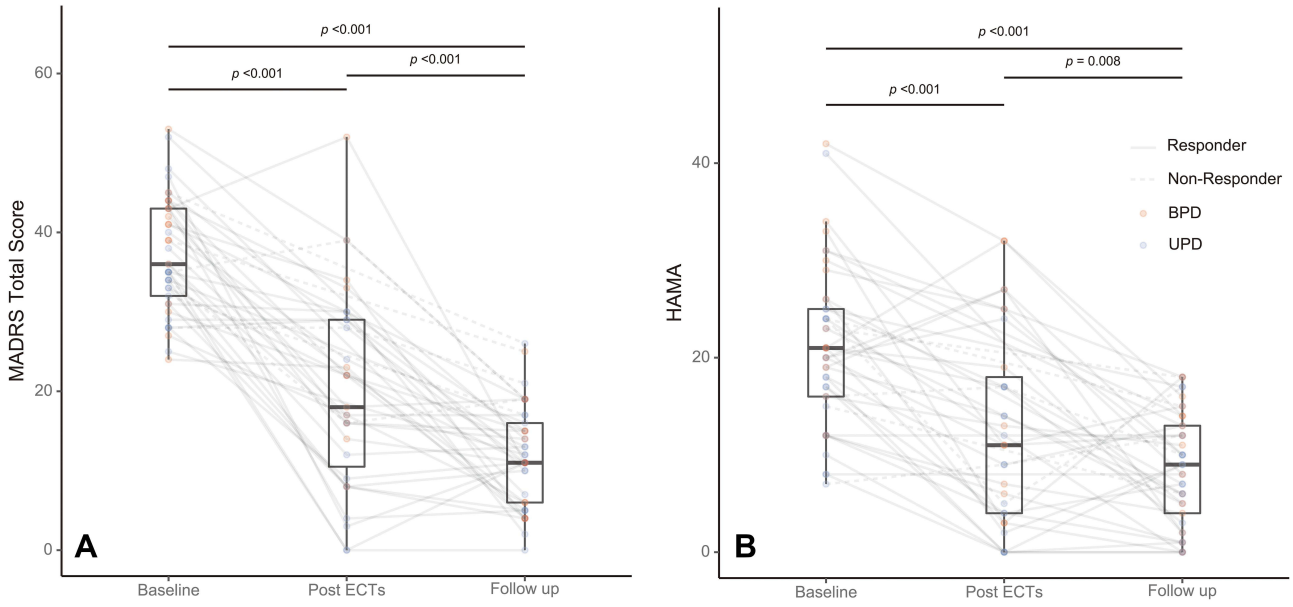

Figure 2 MADRS and HAMA at baseline, post-ECT, and at follow-up. (**A**) Total Montgomery-Äsberg Depression Rating Scale (MADRS) score and (**B**) total Hamilton Anxiety Rating Scale (HAMA) score of Cohort 1 at baseline, post electroconvulsive therapy (ECT), and at follow-up. The pairwise comparisons between the three visits are all statistically significant (details are shown in Table 2).
Abbreviations: UPD, unipolar depression; BPD, bipolar depression.

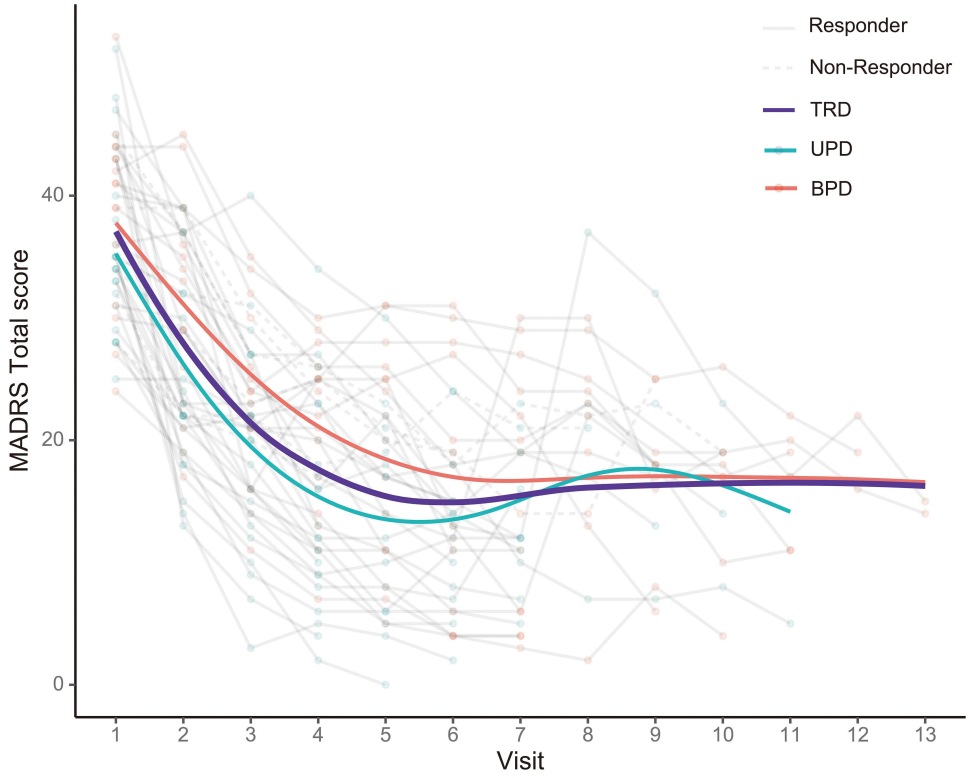

Figure 3 Trajectory of MADRS. The Montgomery-Äsberg depression rating scale (MADRS) total score trajectory during the course of electroconvulsive therapy (ECT) treatment in Cohort 1. The reductions in total MADRS scores at each post-ECT visit from baseline are all statistically significant, but the between-subgroup differences (unipolar depression (UDP) versus bipolar depression (BPD)) were not significant (see Table S4).

For SMI, 34 patients reported varying degrees of subjective cognitive impairment at different visits, and 19 patients reported persistent SMI at the follow-up visit. In the CLMM analysis, SMI significantly increased during ECT (OR = 3.20 (95% CI = 2.38, 4.28; $Z = 7.817$, $p < 0.001$)).

With respect to the trajectory of objective memory function during ECT, as there was a significant practice effect of FDST in the HC group, we focused not only on the within-group change but also the interaction effect size between

Table 3 Estimated Least Squares Mean Effect Size of RBANS Based on MMRM

	TRD	Subgroup Analyses			
		UPD	BPD	Between-Subgroup Difference	
Change from Baseline	**Mean [95% CI]**	**Mean [95% CI]**	**Mean [95% CI]**	**Mean [95% CI]**	***p***
RBANS Total score					
Post ECT[a]	6.0 [−10.4, 22.3]	10.6 [−8.7, 30.0]	1.3 [−23.2, 25.9]	−9.3 [−39.1, 20.5]	0.529
Follow up[b]	32.3 [13.0, 51.7]**	43.2 [19.0, 67.4]***	21.5 [−6.6, 49.6]	−21.7 [−57.0, 13.5]	0.220
Immediate Memory					
Post ECT	7.5 [2.2, 12.8]**	9.3 [3.0, 15.5]**	5.7 [−2.3, 13.7]	−3.6 [−13.2, 6.0]	0.453
Follow up	9.2 [3.0, 15.3]**	13.9 [6.4, 21.5]***	4.4 [−4.6, 13.4]	−9.6 [−20.8, 1.7]	0.093
Visuospatial/Constructional					
Post ECT	2.6 [−2.0, 7.1]	6.2 [0.5, 11.9]*	−1.0 [−7.9, 5.9]	−7.2 [−16.0, 1.5]	0.103
Follow up	3.9 [−2.0, 9.8]	4.7 [−2.8, 12.3]	3.1 [−5.4, 11.6]	−1.6 [−12.5, 9.2]	0.764
Language					
Post ECT	−5.1 [−7.9, 0.5]	−8.1 [−15.2, −1.0]*	−2.2 [−10.7, 6.4]	6.0 [−4.7, 16.7]	0.264
Follow up	2.4 [−4.9, 9.8]	0.6 [−8.7, 10.0]	4.3 [−6.4, 14.9]	3.4 [−10.0, 17.2]	0.592

(*Continued*)

Table 3 (Continued).

	TRD	Subgroup Analyses			
		UPD	BPD	Between-Subgroup Difference	
Change from Baseline	**Mean [95% CI]**	**Mean [95% CI]**	**Mean [95% CI]**	**Mean [95% CI]**	***p***
Attention					
Post ECT	−0.2 [4.2, 3.9]	1.0 [−4.0, 6.1]	−1.4 [−7.3, 4.5]	−2.4 [−9.8, 5.0]	0.517
Follow up	5.5 [0.2, 10.7]*	10.2 [3.5, 16.8]**	0.8 [−6.6, 8.3]	−9.3 [−18.8, 0.2]	0.054
Delayed Memory					
Post ECT	2.0 [−4.6, 8.5]	0.8 [−7.0, 8.6]	3.1 [−6.8, 13.0]	2.3 [−9.7, 14.3]	0.703
Follow up	11.2 [3.2, 19.2]**	12.8 [2.6, 23.1]**	9.5 [−2.0, 21.1]	−3.3 [−18.1, 11.5]	0.653

Notes: [a]Six UPD and three BPD patients did not complete the RBANS. [b]Ten UPD and six BPD patients did not complete the RBANS. Degrees-of-freedom method: Kenward-Roger approach. P value adjustment: Tukey method, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
Abbreviations: MMRM, mixed model for repeated measures; TRD, treatment-resistant depression; UPD, unipolar depression; BPD, bipolar disorder; CI, confidence interval; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

groups. As shown in Figure 5, Figure S4, and Tables S5 and S6, the between-group differences were non-significant at most visits, except for visits 7 and 11. However, in subgroup analyses, the between-subgroup differences were non-significant after correction.

Safety Results

No SAEs occurred during the trial. One hundred and ten common AEs were recorded, with the top AEs being headaches (61 events), muscle aches (28 events), and nausea (7 events).

Data Availability Statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Discussion

This is the first trial presenting detailed observations of the efficacy, speed of response, and cognitive changes of ECT in young adults with TRD. Our trial had two main findings. First, the effect size of ECT was large, with 85.4% of patients with TRD responding to an acute course of ECT and the largest improvements occurring during the first 3–4 ECT sessions. Second, there was a discrepancy between subjective and objective cognitive outcomes during ECT, with patients presenting with more subjective than objective cognitive adverse effects of ECT.

Efficacy

The severity of depression and anxiety was clinically and statistically reduced after ECT. These results were consistent over different outcomes including MADRS subscales and HAMA, and the difference in efficacy between UPD and BPD was non-significant. These findings are consistent with previous studies in young adults,[26,27] although the current response rate (85%) was slightly higher.[24,51] This may be because the patients in our trial suffered from more severe depression combined with a higher rate of psychotic symptoms, which may predict particularly good ECT responses compared with patients with mild-to-moderate depression.[52]

Our repeated symptom assessment revealed that the largest clinical improvements occurred during the first 3–4 ECT sessions for most patients, with a plateau of response after approximately four ECT sessions. The MADRS trajectories were similar in the UPD and BPD subgroups. This finding is consistent with previous studies showing that ECT resulted in a rapid decline in depressed symptom ratings over the early course of treatment and that the symptom change was non-linear,[53,54] which might represent a common pattern of depression relief from ECT, regardless of depression type, treatment sensitivity, severity, and electrode placement. We previously proposed a simple but completely novel ECT protocol involving low-charge electrotherapy (Hybrid-ECT),[55] and our pilot trial showed that Hybrid-ECT may have

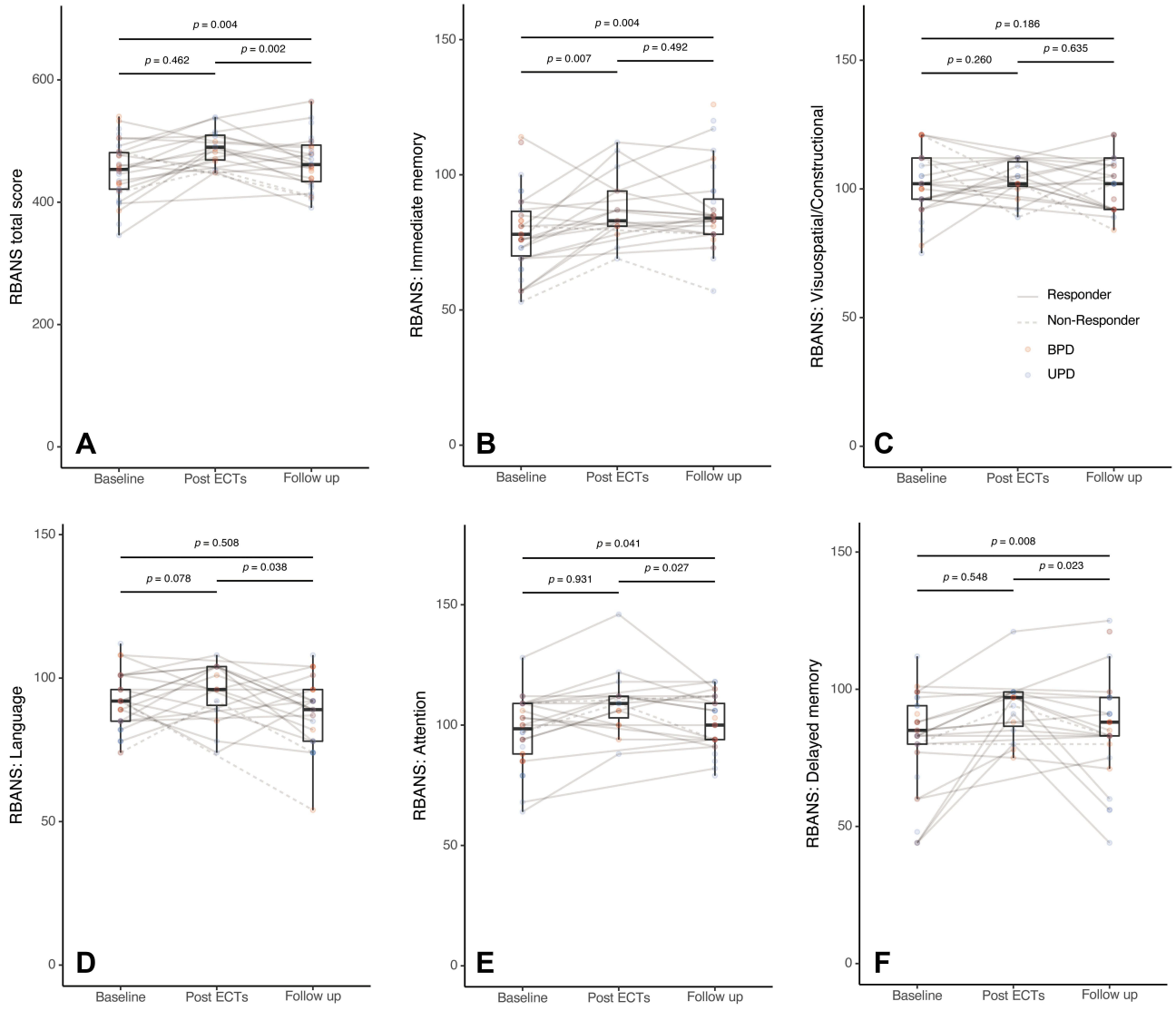

Figure 4 RBANS at baseline, post-ECT, and at follow-up. (**A**) Total Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) score and (**B**–**F**) RBANS subscales for Cohort 1 at baseline, post electroconvulsive therapy (ECT), and at follow-up (details are shown in Table 3).

similar antidepressant effects but with fewer side-effects.[56] We hope there will be more studies developing new ECT protocols that exploit the characteristics of the non-linear symptom relief curve.

Existing data suggest that the long-term outcomes of ECT are poor.[57,58] Over half of patients with depression relapsed by one year following successful initial treatment with ECT, with the majority relapsing within the first six months.[57] Our data show that nearly two-thirds of patients who respond to acute ECT relapsed after one month regardless of subtype, as previously reported.[59] Although most patients received continuation pharmacotherapy, relapse rates following ECT are disappointingly high. Young adults with TRD are vulnerable to relapsing depression related to life stresses including separation, individuation, and identity formation.[12] It has been reported that continuation or maintenance of ECT might prevent depression recurrence after initial response to ECT.[59,60]

Subjective and Objective Cognitive Function

The cognitive side-effects of ECT, especially memory impairment, have received a lot of attention.[46,61–65] We evaluated subjective and objective cognitive function after every ECT and found an unexpected discrepancy between subjective and objective cognitive outcomes, similar to a recent study.[64]

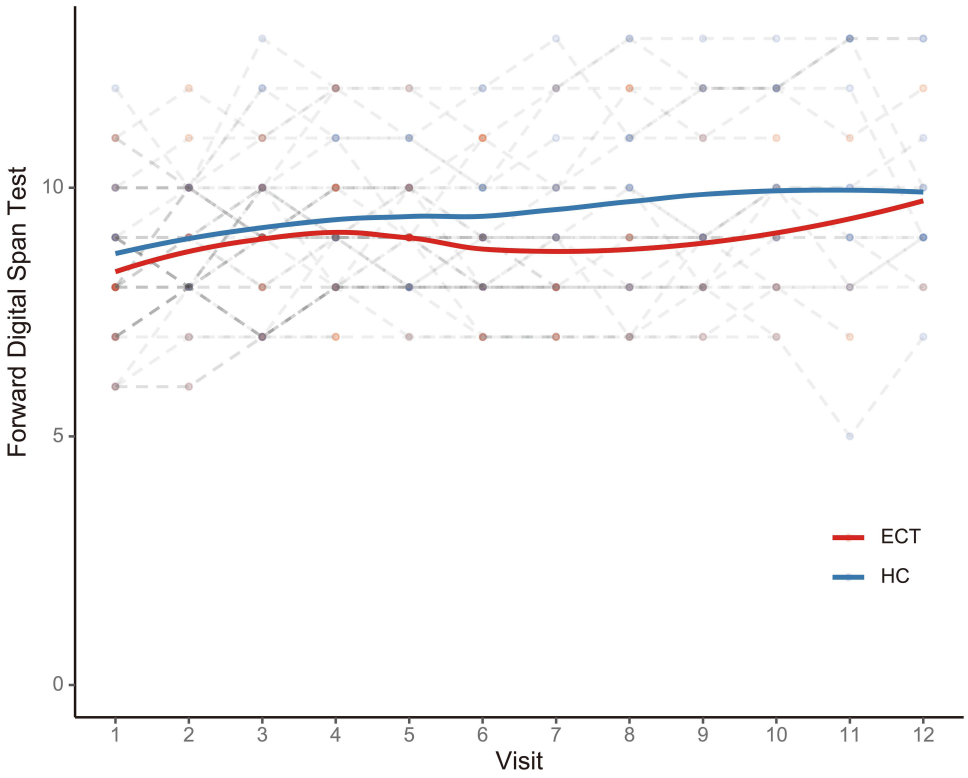

Figure 5 Trajectory of FDST. The Digital Span Test (FDST) trajectory during electroconvulsive therapy (ECT) treatment in Cohort 2. The between-group differences are non-significant at most visits, except for visits 7 and 11 (see Tables S5 and S6).

By exploiting repeated evaluation, we found that subjective cognitive complaints significantly increased during ECT and were still present at one-month follow-up. This result is consistent with a recent study showing that the number of ECT was associated with subjective cognition: more sessions received, higher prevalence of complaints.[45] Furthermore, subjective cognitive complaints did not decrease over time following treatment.[45] There are several possible reasons. First, we used bitemporal ECT, which is usually considered to be associated with more cognitive effects than unilateral ECT.[45] Second, younger patients with more depressive symptoms overreported cognitive impairments.[64,66,67] The patients in our study were young adults who have greater access to the media and internet and who may have learned about the side-effects of ECT to negatively affect their expectations. This expectation may also have induced a "nocebo effect", a negative effect of a pharmacological or non-pharmacological treatment due to patient expectations.[68] Third, younger patients may be more concerned about cognitive deficits because they impede educational attainment and occupational and interpersonal functioning.[69] In addition, patients with TRD and a longer disease course may experience more failures related to cognitive abilities, which may maintain negative self-perceptions that exacerbate their perceived cognitive difficulties.[70]

Conversely, for objective cognitive function, there were no significant changes after ECT treatment as measured with the total RBANS score and visuospatial/constructional, language, and attention subscales. Not only that, there was a significant and consistent increase in memory as measured by the FDST and RBANS subscales, including immediate and delayed memory. Consistent with our results, some studies have also detected improvements in several cognitive domains after ECT,[61–63] although many have similarly detected acute reduced cognition.[27,65,71] These conflicting results may be for several reasons. First, a brief stimulus may significantly reduce adverse cognitive effects,[62,72] especially with an ultra-brief pulse of no more than 0.5 ms.[61,62] Second, ECT increases hippocampal neurogenesis in adults.[73–75] Young adults may have more hippocampal neurogenesis after ECT than older individuals.[73] Neurogenesis-mediated inhibition reduces memory interference and enables reversal learning in both neutral and emotionally charged situations. This increased cognitive flexibility in turn may help reduce anxiety- and depression-like behaviors.[74]

However, the improvement in objective memory was not linear. The FDST trajectory in the TRD group had a slight "S"-shape: increasing over the first 4 visits, decreasing from visits 5–7, and then increasing again. The decrease from visits 5–7 in TDR patients may be due to a cumulative effect of repeated ECT sessions. ECT-induced neurogenesis may lead to abnormal clearance of old memories or a failure to form new memories in the hippocampus, subsequently disrupting memory processes and storage.[76,77] We speculate that this may be the reason why there was a slight decline in memory in the later stages of ECT, even though objective memory after the entire course of ECT was significantly better than baseline.

Furthermore, in the follow-up phase, patients showed significantly improved objective cognition than during acute ECT in terms of total RBANS score and the immediate memory, attention, and delayed memory sub-scores. These results are in keeping with previous studies showing that working memory and some aspects of executive function improved beyond baseline after two weeks posttreatment.[65,78] In short, the impact and mechanisms of ECT on memory deserve further detailed exploration.

Limitations

There are limitations that mean care should be taken extrapolating our conclusions. The cognitive measurements after ECT were relatively simple, due to the difficulty in implementation and limited energy of patients. Another likely explanation for the subjective memory impairment results was that retrograde memory functioning was not assessed. This is the cognitive side effect of ECT and also limitation to the current study. Furthermore, we found a practice effect for FDST, which may counteract the cognitive impairment associated with ECT, considering the possibility of drop-out at follow-up and difficulties in trial implementation, we selected age-, sex-, and education-matched HCs to adjust for the practice effect. The absence of "no-ECT" depression group is another limitation; however, given that this was a group of drug-resistant patients with limited medication changes while receiving ECT, it is unlikely that changes in antidepressant medication had significant impacts on the main results. Furthermore, about 25% of patients were lost to follow-up at one month, mainly due to the COVID-19 pandemic. We had no detailed neurological status for these patients, which could have had a major impact on cognitive status.

Conclusion

ECT is an effective treatment for young adults with TRD. Although there was an increase in SMI with treatment, objective impairments in cognition were not observed. We also recommend using repeated evaluation in future studies to detect subtle changes related to ECT. Clinicians can inform patients about the characteristics of cognitive adverse effects of ECT. They may experience more subjective cognition problems than objective cognition. On this basis, they may need more subjective cognitive training.

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Disclosure

The authors declare that there is no conflict of interest in this work.

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